

What is claimed:

1. A method for regulating a cell-mediated immune response, comprising administering:

- a. a first agent which blocks a CD28/CTLA4/B7-mediated signal by binding CD28, CTLA4 or B7;
- b. a second agent which blocks a CD40/CD154-mediated signal by binding either CD40 or CD154; and
- c. a third agent which blocks an adhesion molecule-mediated interaction by binding to LFA-1, ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1,

whereby blocking by the first, second and third agents regulates a cell-mediated immune response.

2. A method for treating an immune system disease by regulating a cell-mediated immune response by the method of claim 1.

3. A method for inhibiting an immune system disease in a subject comprising administering to a subject:

- a. a first agent which blocks a CD28/CTLA4/B7-mediated signal by binding CD28, CTLA4 or B7;
- b. a second agent which blocks a CD40/CD154-mediated signal by binding either CD40 or CD154; and
- c. a third agent which blocks an adhesion molecule-mediated interaction by binding to LFA-1, ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1,

whereby blocking the first, second and third agents inhibits an immune system disease.

4. A method for inhibiting transplant rejection in a subject, comprising administering to a subject having a transplant:

- a. a first agent which blocks a CD28/CTLA4/B7-mediated signal by binding CD28, CTLA4 or B7;
- b. a second agent which blocks a CD40/CD154-mediated signal by binding either CD40 or CD154; and
- 5 c. a third agent which blocks an adhesion molecule-mediated interaction by binding to LFA-1, ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1,

whereby blocking the first, second and third agents inhibits a cell-mediated immune response to the transplant rejection.

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5. The method of claim 1, 3 or 4, wherein the first agent binds a B7 and is a soluble CTLA4 molecule, a soluble CD28 molecule, or an anti-B7 monoclonal antibody; wherein the first agent binds a CTLA4 and is an anti-CTLA4 monoclonal antibody or a soluble B7 molecule; and/or wherein the first agent binds a CD28 and is an anti-CD28 monoclonal antibody or a soluble B7 molecule.

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6. The method of claim 5, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monoclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is ATCC HB 11944 or mAb 9.3.

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7. The method of claim 1, 3 or 4, wherein the second agent binds a CD154 and is an anti-CD154 monoclonal antibody, and/or wherein the second agent binds CD40 and is an anti-CD40 monoclonal antibody.
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8. The method of claim 7, wherein the anti-CD154 monoclonal antibody is MR1, ATCC HB-10916, ATCC HB-12055 or ATCC HB-12056 and wherein the anti-CD40 monoclonal antibody is ATCC HB-9110.
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9. The method of claim 1, 3 or 4, wherein the third agent binds LFA1 and is an anti-LFA-1 monoclonal antibody; wherein the third agent binds ICAM-1 and is an anti-ICAM-1 antibody; wherein the third agent binds ICAM-2 and is an anti-ICAM-2 antibody; wherein the third agent binds ICAM-3 and is an anti-ICAM-3 antibody; wherein the third agent binds  $\alpha$ -actinin and is an anti- $\alpha$ -actinin antibody; wherein the third agent binds filamin and is an anti-filamin antibody; wherein the third agent binds cytohesin-1 and is an anti-cytohesin-1 antibody; wherein the third agent binds CD18 and is an anti-CD18 antibody; and/or wherein the third agent binds CD11a and is an anti-CD11a antibody.

10. The method of claim 1, 3 or 4, wherein the third agent binds any of ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1 and is a soluble LFA-1; and/or wherein the third agent binds to LFA-1 and is soluble ICAM-1, soluble ICAM-2, soluble ICAM-3, soluble  $\alpha$ -actinin, soluble filamin or soluble cytohesin-1.

11. The method of claim 10, wherein the anti-LFA-1 monoclonal antibody is ATCC HB-9579 or ATCC TIB-213; wherein the anti-ICAM-1 monoclonal antibody is ATCC CRL-1878 or ATCC HB-233; wherein the anti-CD11a monoclonal antibody is M17/5.2 (ATCC TIB-237), ATCC HB-202, ATCC HB-244 or ATCC TIB-217; wherein the anti-CD18 monoclonal antibody is ATCC HB-203, ATCC HB-226 or ATCC TIB-218; and wherein the anti- $\alpha$ -actinin monoclonal antibody is ATCC CRL-2252.

12. The method of claim 1, 3 or 4, wherein the third agent which blocks the adhesion molecule-mediated interaction blocks an LFA-1/ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin, cytohesin-1 interaction.

13. The method of claim 2 or 3, wherein an immune system disease is selected from the group consisting of graft versus host disease (GVHD), psoriasis, immune

disorders associated with graft transplant rejection, T cell lymphoma, T cell acute lymphoblastic leukemia, testicular angiocentric T cell lymphoma, benign lymphocytic angiitis, lupus (e.g. lupus erythematosus, lupus nephritis), Hashimoto's thyroiditis, primary myxedema, Graves' disease, pernicious anemia, autoimmune atrophic gastritis, Addison's disease, diabetes (e.g. insulin dependent diabetes mellitis, type I diabetes mellitis), good pasture's syndrome, myasthenia gravis, pemphigus, Crohn's disease, sympathetic ophthalmia, autoimmune uveitis, multiple sclerosis, autoimmune hemolytic anemia, idiopathic thrombocytopenia, primary biliary cirrhosis, chronic action hepatitis, ulceratis colitis, Sjogren's syndrome, rheumatic diseases (e.g. rheumatoid arthritis), polymyositis, scleroderma, and mixed connective tissue disease.

14. The method of claim 1, 3 or 4, wherein the first, second and third agents are administered locally or systemically.

15. The method of claim 1, 3 or 4, wherein the first, second and third agents are administered sequentially or concurrently and in any order.

16. The method of claim 3 or 4, wherein the subject is selected from the group consisting of human, monkey, ape, dog, cat, cow, horse, rabbit, mouse and rat.

17. A method for regulating an immune system disease by blocking a cell-mediated immune response with:

a. a first agent which is a soluble CTLA4; and

b. a second agent which is an anti-CD154 monoclonal antibody; and

d. a third agent which is an anti-LFA-1 monoclonal antibody,

whereby the first, second and third agents inhibits the cell-mediated immune disease.

18. A method for inhibiting allograft transplant rejection by blocking a cell-mediated immune response with:

a. a first agent which is a soluble CTLA4; and  
b. a second agent which is an anti-CD154 monoclonal antibody; and  
c. a third agent which is an anti-LFA-1 monoclonal antibody,  
wherein the first, second and third agents inhibits the cell-mediated immune  
response to the transplant.

19. A pharmaceutical composition comprising a first, second and third agent, and  
wherein

- a. the first agent blocks a CD28/CTLA4/B7-mediated signal by binding  
CD28, CTLA4 or B7,  
b. the second agent blocks a CD40/CD154-mediated signal by binding either  
CD40 or CD154, and  
c. the third agent blocks an LFA-1/ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin,  
filamin or cytohesin-1 interaction.

20. A kit for treating transplant rejection, said kit comprising an effective amount of a  
first agent, a second agent and a third agent, and

- a. the first agent blocks a CD28/CTLA4/B7-mediated signal by binding  
CD28, CTLA4 or B7;  
b. the second agent blocks a CD40/CD154-mediated signal by binding either  
CD40 or CD154; and  
c. the third agent blocks an LFA-1/ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin,  
filamin or cytohesin-1 interaction.

21. The pharmaceutical composition of claim 19 further comprising at least one  
immunosuppressive agent, wherein the immunosuppressive agent is selected from  
the group consisting of corticosteroids, nonsteroidal antiinflammatory drugs (e.g.  
Cox-2 inhibitors), cyclosporin prednisone, azathioprine, methotrexate, TNF $\alpha$   
blockers or antagonists, infliximab, any biological agent targeting an  
inflammatory cytokine, hydroxychloroquine, sulphasalazopyrine, gold salts,  
etanercept, and anakinra.

22. The pharmaceutical composition of claim 19, wherein the first agent binds a B7 and is a soluble CTLA4 molecule, a soluble CD28 molecule, or an anti-B7 monoclonal antibody; wherein the first agent binds a CTLA4 and is an anti-CTLA4 monoclonal antibody or a soluble B7 molecule; and/or wherein the first agent binds a CD28 and is an anti-CD28 monoclonal antibody, or a soluble B7 molecule.

23. The pharmaceutical composition of claim 22, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monoclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is ATCC HB 11944 or mAb 9.3.

24. The pharmaceutical composition of claim 19, wherein the second agent binds a CD154 and is an anti-CD154 monoclonal antibody, and/or wherein the second agent binds CD40 and is an anti-CD40 monoclonal antibody.

25. The pharmaceutical composition of claim 24, wherein the anti-CD154 monoclonal antibody is MR1, ATCC HB-10916, ATCC HB-12055 or ATCC HB-12056 and wherein the anti-CD40 monoclonal antibody is ATCC HB-9110.

26. The pharmaceutical composition of claim 19, wherein the third agent binds LFA1 and is an anti-LFA-1 monoclonal antibody; wherein the third agent binds ICAM-1 and is an anti-ICAM-1 antibody; wherein the third agent binds ICAM-2 and is an anti-ICAM-2 antibody; wherein the third agent binds ICAM-3 and is an anti-ICAM-3 antibody; wherein the third agent binds  $\alpha$ -actinin and is an anti- $\alpha$ -actinin antibody; wherein the third agent binds filamin and is an anti-filamin antibody; wherein the third agent binds cytohesin-1 and is an anti-cytohesin-1 antibody;

wherein the third agent binds CD18 and is an anti-CD18 antibody; and/or wherein the third agent binds CD11a and is an anti-CD11a antibody.

27. The pharmaceutical composition of claim 19, wherein the third agent binds any of ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1 and is a soluble LFA-1; and/or wherein the third agent binds to LFA-1 and is soluble ICAM-1, soluble ICAM-2, soluble ICAM-3, soluble  $\alpha$ -actinin, soluble filamin or soluble cytohesin-1.

28. The pharmaceutical composition of claim 27, wherein the anti-LFA-1 monoclonal antibody is ATCC HB-9579 or ATCC TIB-213; wherein the anti-ICAM-1 monoclonal antibody is ATCC CRL-1878 or ATCC HB-233; wherein the anti-CD11a monoclonal antibody is M17/5.2 (ATCC TIB-237), ATCC HB-202, ATCC HB-244 or ATCC TIB-217; wherein the anti-CD18 monoclonal antibody is ATCC HB-203, ATCC HB-226 or ATCC TIB-218; and wherein the anti- $\alpha$ -actinin monoclonal antibody is ATCC CRL-2252.

29. The kit of claim 20 further comprising at least one immunosuppressive agent, wherein the immunosuppressive agent is selected from the group consisting of corticosteroids, nonsteroidal antiinflammatory drugs (e.g. Cox-2 inhibitors), cyclosporin prednisone, azathioprine, methotrexate, TNF $\alpha$  blockers or antagonists, infliximab, any biological agent targeting an inflammatory cytokine, hydroxychloroquine, sulphasalazopyrine, gold salts, etanercept, and anakinra.

30. The kit of claim 20, wherein the first agent binds a B7 and is a soluble CTLA4 molecule, a soluble CD28 molecule, or an anti-B7 monoclonal antibody; wherein the first agent binds a CTLA4 and is an anti-CTLA4 monoclonal antibody or a soluble B7 molecule; and/or wherein the first agent binds a CD28 and is an anti-CD28 monoclonal antibody or a soluble B7 molecule.

31. The kit of claim 30, wherein the soluble CTLA4 molecule is CTLA4Ig (ATCC 68629) or L104EA29YIg (ATCC PTA-2104); wherein the soluble CD28 molecule is CD28Ig (ATCC 68628); wherein the soluble B7 molecule is B7Ig (ATCC 68627); wherein the anti-B7 monoclonal antibody is ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301 or ATCC HB-11341; wherein the anti-CTLA4 monoclonal antibody is ATCC HB-304; and wherein the anti-CD28 monoclonal antibody is ATCC HB 11944 or mAb 9.3.

32. The kit of claim 20, wherein the second agent binds a CD154 and is an anti-CD154 monoclonal antibody, and/or wherein the second agent binds CD40 and is an anti-CD40 monoclonal antibody.

33. The kit of claim 32, wherein the anti-CD154 monoclonal antibody is MR1, ATCC HB-10916, ATCC HB-12055 or ATCC HB-12056 and wherein the anti-CD40 monoclonal antibody is ATCC HB-9110.

34. The kit of claim 20, wherein the third agent binds LFA1 and is an anti-LFA-1 monoclonal antibody; wherein the third agent binds ICAM-1 and is an anti-ICAM-1 antibody; wherein the third agent binds ICAM-2 and is an anti-ICAM-2 antibody; wherein the third agent binds ICAM-3 and is an anti-ICAM-3 antibody; wherein the third agent binds  $\alpha$ -actinin and is an anti- $\alpha$ -actinin antibody; wherein the third agent binds filamin and is an anti-filamin antibody; wherein the third agent binds cytohesin-1 and is an anti-cytohesin-1 antibody; wherein the third agent binds CD18 and is an anti-CD18 antibody; and/or wherein the third agent binds CD11a and is an anti-CD11a antibody.

35. The kit of claim 20, wherein the third agent binds any of ICAM-1, ICAM-2, ICAM-3,  $\alpha$ -actinin, filamin or cytohesin-1, and is a soluble LFA-1 or wherein the third agent binds to LFA-1 and is soluble ICAM-1, soluble ICAM-2, soluble ICAM-3, soluble  $\alpha$ -actinin, soluble filamin or soluble cytohesin-1.



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36. The kit of claim 35, wherein the anti-LFA-1 monoclonal antibody is ATCC HB-9579 or ATCC TIB-213; wherein the anti-ICAM-1 monoclonal antibody is ATCC CRL-1878 or ATCC HB-233; wherein the anti-CD11a monoclonal antibody is M17/5.2 (ATCC TIB-237), ATCC HB-202, ATCC HB-244 or ATCC TIB-217; wherein the anti-CD18 monoclonal antibody is ATCC HB-203, ATCC HB-226 or ATCC TIB-218; and wherein the anti- $\alpha$ -actinin monoclonal antibody is ATCC CRL-2252.